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A Comparative Evaluation of Cyclin D1 Expression in Various Grades of Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma Using Immunohistochemistry

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ABSTRACT: Oral epithelial dysplasia is a diagnostic term that has been used to describe the histopathological changes seen in potentially malignant disorders which are the precursor lesions of oral squamous cell carcinoma.Cyclin D1 has been strongly implicated in the cell proliferation in the G1-S check point of the eukaryoytic cell cycle ,it is positively regulated by cyclins and negatively regulated by the inhibitors of cyclin dependent kinases. We designed a study by using the surrogate marker cyclin D1 in the true prediction of malignant potential and molecular mutation in oral potentially malignant disorders

KEYWORDS: Oral epithelial dysplasia, OSCC, cyclin D1,immunohistochemistry.

I. INTRODUCTION

The multistage process of carcinogenesis involves acquisition of mutations and epigenetic abnormalities in the expression of multiple genes, with an important group among them being those involved in cell cycle control.[1] The orderly progression of cells through the various phases of cell cycle is governed by the namely, G1, S, G2, and M phases is precisely governed by a series of proteins called “cyclins,” which exert their effect by binding and activating the cyclin-dependent kinases (CDK).[2]

Cyclin D1 is a proto-oncogene encoding a positive regulator of g1 phase progression through the cell cycle that regulates the initiation of DNA synthesis. [3]Over expression of Cyclin D1 results in the progression through the G1 phase of cell cycle in the absence of extracellular mitogen stimulation..[1] Its a 45 kd (kilo Dalton) protein encoded by Cyclin D1 gene (ccnd1) located on chromosome 11q13, is a part of the molecular system that regulates the cell cycle g1 to s transition. It was first isolated as parathyroid adenomatosis 1 gene (prad1) oncogene clonally rearranged and overexpressed in parathyroid adenomas and is identical to B-cell lymphoma1 gene (bcl-1) protooncogene, which is translocated and overexpressed in a subset of B-cell neoplasms.[4]

Overexpression of Cyclin D1 leads to shortening of G1 phase and less dependency on growth factors resulting in abnormal cell proliferation which in turn might favour the occurrence of additional genetic lesions.[1]Overexpression of Cyclin D1 has been reported in 25-30% of oral cancers and high percentage of premalignant lesions suggesting that Cyclin D1 gene amplification and consequent protein expression are early events during oral tumorigenesis.[1] so in order to determine the prognostic significance of cyclinD1 in the risk of malignant transformation of Oral Epithelial Dysplasia, we designed a study by comparing the expression of Cyclin D1 in different grades of dysplasia ,OSCC and normal mucosa.

Aims: To compare Cyclin D1 expression in various grades of Oral Epithelial Dysplasia, Oral Squamous Cell Carcinoma and normal mucosa**.**

II. SETTINGS AND DESIGN:

A retrospective study on patients with Oral Epithelial Dysplasia and OSCC was carried out during the period from June 2017 to June 2019.

III. METHODS ANDMATERIAL:

Cyclin D1 expression was evaluated and studied in 50 tissue samples

.Statistical analysis used:Descriptive statistics were used to summarize the sample characteristics and clinical variables. If the data

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were normal, then parametric tests were used; otherwise, nonparametric alternatives were used. All the analyses were carried out using SPSS version 23.0 (IBM SPSS Inc., USA).

X. Results: Our study showed that the expression of cyclin D1 in OSCCS where significantly higher as compared to Oral Epithelial Dysplasia and normal mucosa with p value <0.001. when we compared the expression of cyclin D1 in various grades of OED ,we found that a statistical correlation with p value <0.001. Cyclin D1 positivity was seen in 40 cases of Oral Epithelial Dysplasia and OSCC. Further distribution of cyclin D1 reactivity in accordance with site, are explained in Table 1. The labelling index scores, intensity of staining, expressions graded, and their correlations with clinical and histological parameters are elaborated in Table 2. Both cyclin D1 reactivity and expression did not show any correlation with site and clinical staging of the OSCC (Tables 1 and 3). The histopathological differentiation showed a positive correlation with increase in both the reactivity and expression with increasing differentiation (Tables 1 and 3). The labelling index score and intensity did not correlate with OSCC differentiation (Table 2)

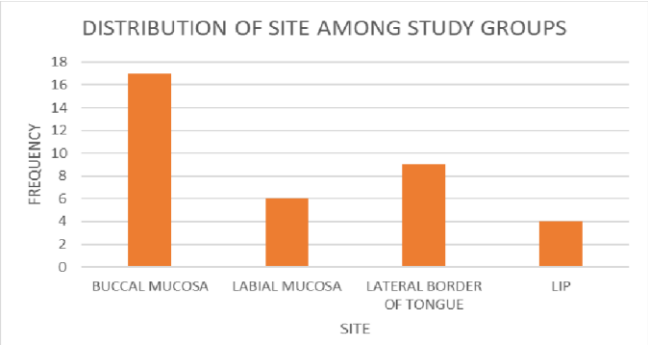

TABLE1 DISTRIBUTION OF SITE AMONG STUDY GROUPS

Grades of Dysplasia	Intensity				
	Negative	Mild Intensity	Moderate Intensity	Severe Intensity	Total
Mild epithelial dysplasia	7 (70 %)	3 (30%)	0 (0%)	0 (0%)	10 (100%)
Moderate epithelial Dysplasia	0 (0%)	3 (30%)	5 (50%)	2 (20%)	10 (100%)
Severe Epithelial dysplasia	0 (0%)	0 (0%)	3 (30%)	7 (70%)	10 (100%)
Total	7 (23.3 %)	6 (20%)	8 (26.7%)	9 (30%)	30 (100%)

Study Groups	Intensity				
	Negative Intensity	Mild Intensity	Moderate Intensity	Severe Intensity	Total
Oed	7 (23.3%)	6 (20%)	8 (26.7%)	9 (30%)	30 (100%)
Oscc	0 (0%)	2 (20%)	3 (30%)	5 (50%)	10 (100%)
Normal Mucosa	7 (70%)	3 (30%)	0 (0%)	0 (0%)	10 (100%)
Total	14 (28%)	11 (22%)	11 (22%)	14 (28%)	50 (100%)

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TABLE 3:**COMPARISON OF INTENSITY OF STAINING IN DIFFERENT GRADES OF ORAL EPITHELIAL DYSPLASIA AND ORAL SQUAMOUS CELL CARCINOMA**

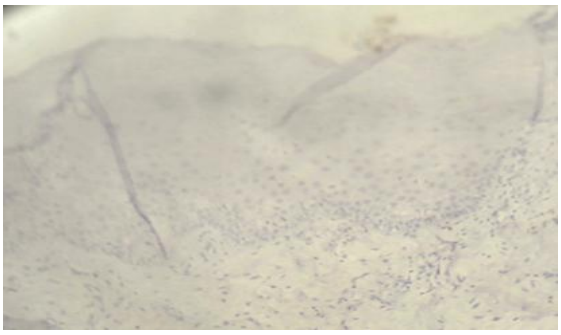

FIGURE 1:NEGATIVE STAINING IN MILD DYSPLASIA

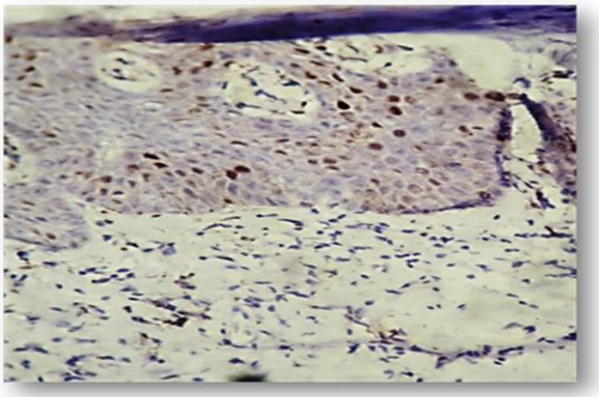

FIGURE 3:POSITIVE STAINING IN SEVERE EPITHELIAL DYSPLASIA

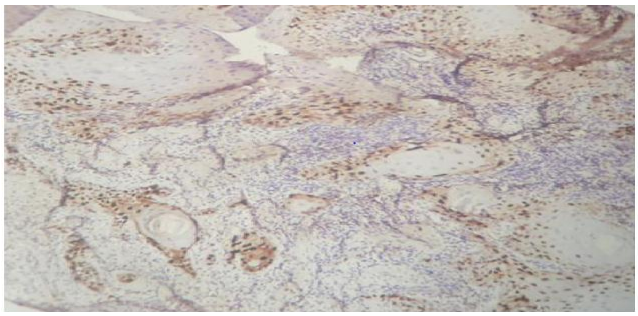

FIGURE 4:POSITIVE STAINING IN ORAL SQUAMOUS CELL CARCINOMA

IV. CONCLUSIONS:

InourstudywefoundcyclinD1expressioninallgradesofOralEpithelialDysplasiaincludingmilddysplasia, which is suggestive of molecular mutations in early precancerous lesions itself. Also, we could find more expression of cyclin D1 in OSCC when compared with Oral Epithelial Dysplasia. Expression of cyclin D1 in mild epithelial dysplasia suggest the risk of development of malignancy in early stages of dysplasia itself at molecular level so we could suggest that there is great variability in the interpretation of WHO Histopathological grading of Oral Epithelial Dysplasia as mild, moderate and severe Dysplasia.

V. DISCUSSION:

Head and neck cancers represent the sixth most common cancer worldwide.More than 90% of the head and neck cancers are squamous cell carcinomas that arise from the mucosal surfaces of

the oral cavity, oropharynx and the larynx.[5]Oral cancer is a major public health problemintheIndianland mass,whereitranksamongthetopthreetypesofcanceri nthecountry.The risk of being diagnosed with cancer increases with age and also with certain risk factors associated with thedisease. Oralsquamouscellcarcinomamayoccurdenovoorfro mprecursorlesions.[6]Iftheprecursor lesion is discovered, diagnosed and monitored, it increases the survival rates and decreases themorbidity associated with oral cancer.[10]Oral epithelial dysplasia is a diagnostic term that is used to describe the histopathological changes seen in potentially malignant disorders of oral mucosa.[7]Leukoplakia, erythroplakia and OSMF are the lesions usually associated with dysplastic changes. TheprognosticevaluationofOralEpithelialDysplasia andOralSquamousCell Carcinoma werefoundtobeinaccurateinlongtermfollowupstudie sduetointerandintraobservervariability.[8]Thus,charac terisation of a malignant disease by tumour markers improves our understanding of variations in theclinicalcasesofindividualpatientsandhelpstoesti matetheirprognosis.[9] Thus we devised our study on cyclin D1 and its not only a prognostic marker bus also a chemotarget.

In our study we found that the expression of cyclin D1 in group 1 was more in severe dysplasia as compared to moderate and mild epithelial dysplasia with p value <0. 005. OSCC (Group 2) showed more expression and intensity of staining than Oral Epithelial Dysplasia with p value <0.005. Normal mucosa showed negligible expression.

Cyclins exert an essential part of the cell cycle control. Cyclin D1 promote tumorigenesis by dysregulation of the cell cycle.[10] It's a fundamental hallmark of cell cycle progression.[11] Deregulated cyclin D1 cannot integrate growth factor signals within the cell cycle machinery leading to shorteningoftheG1phase,increasedcellproliferationa ndreduceddependencyongrowthfactors,which might result in accumulation of non-repaired DNA mutations leading to disturbance in the normal cell cycle and tumor formation.[12]

Onlyfewstudieshaveevaluatedthesignifican ceofcyclinD1inOEDandOSCC.Inour study we found that WHO grading of OED and OSCC is subjective and predictability does not account for the malignant transformation between grades of dysplasia as cyclin D1 expression was found in all gradesofdysplasiawhichissuggestiveofmolecularmu tationsandriskofdevelopmentofmalignancyin early dysplastic lesions. Further studies with larger sample size are required to emphasise the reliability of ourstudy.

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